UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/581,398	08/03/2000	ABDESSATAR CHTOUROU	065691/0193	9759

22428 7590 11/13/2003

FOLEY AND LARDNER
SUITE 500
3000 K STREET NW
WASHINGTON, DC 20007

EXAMINER	
MOHAMED, ABDEL A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 11/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/581,398	CHTOUROU ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-49 and 51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/23/03 has been entered.

ACKNOWLEDGMENT OF PRELIMINARY REMARKS, DECLARATION AND STATUS OF THE CLAIMS

2. The preliminary remarks and declaration filed under 37 C.F.R. § 1.132 on 9/23/03 are acknowledged, entered and considered. Claims 24-49 and 51 are now pending in the application. The rejection under 35 U.S.C. 103(a) over the prior art of record is maintained for the reasons of record.

CLAIM REJECTIONS-35 U.S.C. § 103(a)

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24-49 and 51 remain rejected under 35 U.S.C. 103(a) as being unpatentable over WO 96/00237 taken with Josic et al. (J. Chromatogr. B. Biomed. Appl., Vol. 662, No. 2, pp. 181-190, 1994), Grandgeorge et al (U.S. Patent No. 5,371,195) and Farb et al (U.S. Patent No. 4,758,657).

WO 96/00237 teaches a method of virus-filtering a solution that contains at least one macromolecule, particularly factor VIII which may be native or recombinant, wherein the salt content of the solution lies in the range of from about 0.2 M up to saturation of the solution with the salt concerned (See e.g., abstract, page 5, lines 14 to 24 and claim 1). On page 7, lines 30 to page 9, lines 27, the reference clearly teaches the use of various filters which are readily available commercially such as Planova™ 15 filter for virus filtration having a porosity as low as 15 nm for the intended purpose of reducing the content of very small non-enveloped viruses, such as parvoviruse, polio virus, hepatitis virus, etc. Thus, the primary reference clearly teaches a method for

obtaining a variety of safe solution of the plasma protein complex such as FVIII by a filtration step using a filter with a porosity of 15 nm.

The primary reference of WO 96/00237 differs from claims 24-49 and 51 in not using chaotropic ions such as calcium for dissociation purpose and the purification of the cryoprecipitate fraction of the plasma by ion exchange chromatography. However, Josic et al. teach the purification of FVIII and vWF from human plasma by anion-exchange chromatography, wherein the purification is carried out by a combination of precipitation and chromatographic procedures. After precipitation, the first step in virus inactivation is achieved through the effect of a non-ionic detergent such as Tween 80, and as solvent such as TnBp (i.e., inactivated by solvent/detergent treatment as claimed in claim 41). By anion-exchange chromatography, a highly enriched product consisting of a complex formed by FVIII and vWF is isolated. The second step in virus inactivation is conducted with the addition of stabilizers, pasteurization and subsequent removal by ion-exchange chromatography. The resulting complex of FVIII and vWF are dissociated by adding calcium ions and subsequently both glycoproteins from the complex are separated from one another by further anion-exchange chromatography (See e.g. abstract, pages 183-184 and Figure 1). Thus, clearly teaching the separation of FVIII and vWF using treatment by calcium ions after purification of the FVIII-vWF plasma complex using chromatographic techniques.

Further, Grandgeorge et al (U.S. Patent No. 5,71,195) teaches a method for purifying FVIII from cryoprecipitate, enabling chromatographic yields of more than 90% to be achieved by dissolving FVIII and subjecting to viral inactivation with solvent/detergent and further subjecting to chromatography on a weak anion-exchange column which is hydrophilic in nature and FVIII is then eluted with a dissociating buffer (See e.g. abstract and summary of the invention). Furthermore, Farb et al discloses a

multi-step process for separating FVIII from plasma in which at least one of the steps requires the adsorption of FVIII on a hydrophilic interaction matrix (See e.g. summary of the invention). Moreover, as acknowledged on page 2, lines 23-32 in the instant specification, the elimination of vWF proteins (that is, implicitly, high molecular weight vWF, and therefore, implicitly, free of high molecular weight vWF). Thus in view of this and in view of the teachings of the secondary references, one of ordinary skill in the art could have envisaged filtering the solution of dissociated FVIII/vWF which is obtained as a product which is free of virus and devoid of vWF by combining a filtration and dissociation steps using a filter with a porosity of 15 nm. Therefore, it would have been obvious to one of ordinary skill in the art to apply the teachings of the secondary references to the primary reference because such features are known or suggested in the art, as seen in the secondary references, and including such features into the methods of the primary reference would have been obvious to one of ordinary skill in the art to obtain the known and recognized functions and advantages thereof.

With respect to claim 51, the claim is in product-by-process format and as such, it is the novelty and patentability of the instantly claimed product that need be established and not the recited process steps, In re Brown, 173 USPQ 685 (CCPA 1972); In re Wertheim, 191 USPQ (CCPA 1976). Further, the prior art described the product as old, In re Best, 195 USPQ 430, 433 (CCPA 1977); (See MPEP 706.03 [e]). Hence, the burden of proving that the process limitation makes a different product is shifted to the Applicants, In re Fitzgerald, 205 USPQ 594.

Therefore, in view of the above and in view of the combined teachings of the prior art, one of ordinary skill in the art would have been motivated to employ a method for obtaining a virus free solution of the plasma protein complex of FVIII, said solution essentially being free of high molecular weight vWF and obtained from a solution

containing high molecular weight FVIII-vWF complexes, said method combining a dissociation step and a filtration step using a filter with a porosity of 15 nm., absence of sufficient objective factual evidence or unexpected results to the contrary.

ARGUMENTS ARE NOT PERSUASIVE

CLAIMS REJECTION-35 U.S.C. § 103(a)

4. The rejection of claims 24-49 and 51 under 35 U.S.C. 103(a) as being unpatentable over WO 96/00237 taken with Josic et al. (J. Chromatogr. B. Biomed. Appl., Vol. 662, No. 2, pp. 181-190, 1994), Grandgeorge et al (U.S. Patent No. 5,371,195) and Farb et al (U.S. Patent No. 4,758,657).

Applicant's preliminary remarks and declaration filed 9/23/03 have been fully considered but they are not persuasive. It is noted that Applicant has argued on page 1 of the preliminary remarks filed 9/23/03 that the declaration states that factor VIII (FVIII) of the WO 96/00237 application was a recombinant FVIII, aka r-VIII SQ_3 in which domain B has been deleted (See WO'237, page 5, bottom). When domain B is removed from FVIII, the molecular weight of the molecule drops from 290 kDa to 170 kDa. As stated in WO 96/00237, a Viresolve™/180filter was taught as being suitable for filtering r-VIII SQ_3 because this recombinant protein has a molecular weight of about 170 kDa (See id., page 8, lines 19-20). This does not suggest that a smaller 15 nm filter can be used to effectively filter a natural FVIII molecule of 170 kDa is not persuasive. Contrary to Applicant's arguments, independent claim 24 is directed to a method for preparing, a FVIII solution that is free of viruses and devoid of vWF and FVIII-vWF complexes comprising (a) obtaining a starting FVIII solution devoid of FVIII-vWF complexes; and (b) filtering said solution through a hydrophilic virus filter, wherein the virus filter has a mean pore size of 15 ± 2

nm. However, the limitations Applicant argued with (i.e., recombinant protein has a molecular weight of about 170 kDa) are not recited in the rejected claim(s). Nevertheless, the claims are interpreted in light of the specification, limitations from specification are not read into claims. See In re Van Geuns, 988 F.2nd 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Thus, Applicant's arguments are not commensurate to the scope of the claims. Further, in view of the claim language "comprising" which would not exclude other types of FVIII which include/encompass recombinant FVIII, and in view of dependent claim 43 which states wherein the starting FVIII solution comprises recombinant FVIII. Thus, Applicant's preliminary remarks and declaration which states the main difference between the natural plasma derived FVIII and the B domain deleted recombinant one is related to their respective molecular weights i.e., 290 kDa versus 170 kDa are unpersuasive for the reasons in the above stated rejection and further, the claim formulation clearly suggest or motivate one of ordinary skill in the art the use of any kind of FVIII in the process claimed.

In addition, the declaration asserts that the prior art of record does not suggest or teach the filtration of the natural FVIII on 15 nm having optimal operating conditions such as the presence of $CaCl_2$ (claim 28, appears to be typographical error. The correct one is claim 30); filtration with low pressure (,0.3 bar) claim 33; and filtration at $35^0C \pm 5^0C$ (claim 35). However, such optimal operating conditions, which stipulate the independent claim, should be incorporated in independent claim to define the invention. Thus, incorporating the above limitations into independent claim 24 would be a way to overcome the prior art of record rejection.

5. It is noted that Applicant has not amended the claims after Advisory Action mailed 2/19/03 (Paper No. 14). Although, Applicant has filed a preliminary response and a

declaration on 9/23/03 as Paper No. 17 which was discussed above. However, there is no response to the unamended claims. Thus, the Examiner maintains the rejection since the unamended claims 24-49 and 51 have been rejected previously under 35 U.S.C. 103(a) on Advisory Action as reiterated below:

The rejection under 35 U.S.C. 103(a) over the prior art of record is maintained. Applicant's arguments that the combined teachings of the prior art, particularly the primary reference of WO 96/00237 does not teach the elements of claim 24, does not provide reasonable expectation of success in arriving at the present invention, or suggest the present invention of claim 24, and there is no nexus between the factor VIII (FVIII) and a 15 nm filter, nor any explicit or implicit suggestion that these two features are combinable into a single process, and as such, the prior art of record cannot support a *prima facie* establishment of obviousness is unpersuasive. Although, Applicant has limited independent claim 24 to filtering FVIII solution with virus filter having a mean pore size of 15 nm, however, contrary to Applicant's arguments, the primary reference of WO 96/00237 on page 8, lines 11-12 states that Planova™ 15 is used to remove small viruses, such as polio viruses. Further, on page 8, lines 14-20, the reference states that the choice of filter depends on the size of the protein concerned and recites various proteins having different molecular weights and among them FVIII. Hence, based on the molecular weights and the intended purpose of filtration (i.e., in the instant case, virus filtration of viruses to make FVIII free of virus), one of ordinary skill in the art would be able to determine the appropriate filter size. Thus, the primary reference clearly teaches or suggests the use of various filters which are readily available commercially such as Planova™ 15 filter for virus filtration having a porosity as low as 15 nm for the intended purpose of reducing and/or removing the content of very small

non-enveloped viruses, such as parvoviruse, polio virus, hepatitis virus, etc., in protein solution of interest which may include FVIII.

Therefore, in view of the above and in view of the combined teachings of the prior art, one of ordinary skill in the art would have been motivated to employ a method for obtaining a virus free solution of the plasma protein complex of FVIII by combining a dissociation step and a filtration step using a filter with a porosity of 15 nm in the manner claimed in the instant invention. Thus, it is made obvious by the combined teachings of the prior art since the instantly claimed invention which falls within the scope of the prior art teachings would have been obvious because as held in host of cases including *Ex parte Harris*, 748 O.G. 586; *In re Rosselete*, 146 USPQ 183; *In re Burgess*, 149 USPQ 355 and as exemplified by *In re Betz*, "the test of obviousness is not express suggestion of the claimed invention in any and all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them". Thus, the rejection of claims 24-49 and 51 under 35 U.S.C. 103(a) over the prior art of record is maintained for the same reasons discussed in the previous Office action.

CLAIMS REJECTION-35 U.S.C. § 112 2nd PARAGRAPH

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention

Claim 25-49 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Dependent claims 25-49 are indefinite in the recitation "A method according.....". Since claims 25-49 are dependent claims depending directly or indirectly to claim 24, amendment of the claims to recite "the method according....." would obviate this rejection.

Claim 48 is indefinite in the recitation "A method according to 24". It is believed to be typographical error. Amendment of the claim to recite "The method according to claim 24" is suggested.

Claim 49 is indefinite in the recitation "A method according to 49" because the claim depends on self and also for the reasons discussed on claim 48. Appropriate correction is required.

ACTION IS FINAL, FIRST ACTION FOLLOWING REQUEST FOR CONTINUED EXAMINATION UNDER 37 CFR 1.114

7. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

CONCLUSION AND FUTURE CORRESPONDENCE

8. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (703) 308-3966. The examiner can normally be reached on Monday through Friday from 5:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (703) 308-2923. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

CHRISTOPHER S. F. LOW
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

AAM/Mohamed/AAM

November 11, 2003